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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/733,756	MACK ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6, 8-30,32,33,37,41-47 and 52-57* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 8-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,33,37,41-47 and 52-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed October 10, 2003 and August 13, 2003.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of applicant's arguments, and the amendments to the claims.

4. Claims 32-33, 37, 41-47, 52-57 have been examined on the merits.

5. Claims 1-6, 8-30 have been withdrawn from consideration as drawn to non-elected claims.

Maintained Rejections

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 32-33, 37, 41-47, 52-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining a predisposition of an individual to colorectal cancer by determining the expression of SEQ ID NO: 1 in a first colorectal sample and comparing expression to a normal sample wherein an increase in expression is indicative of colorectal cancer, does not reasonably provide enablement for a method of detecting colorectal or breast cancer by

determining the expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method for diagnosing breast cancer or colorectal cancer by determining the expression level of a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 2.

The specification teaches that SEQ ID NO: 1 corresponds to the gene CHA4. CHA4 nucleic acid and amino acid sequences are shown in Figure 1 and 2, respectively. Example 3, states that expression studies were performed using an oligonucleotide array. The biochip contained the sequence shown in accession number T32108. Figures 3A illustrates the relative amount of expression of CHA4 in various samples of breast cancer tissue; Figure 3B illustrates colorectal cancer tissue; and Figures 3C-3D illustrate several normal tissue types. With respect to Figure 3A directed

to breast cancer tissue, the expression level in the tissues appears to range from 100-750 (no units provided). Turning to Figure 3C, normal breast tissue appears to range from 80-400 (no units provided). As seen in Figure 3A, 54 of the samples had expression within the "normal" range of expression. 54 of the 66 (83%) breast cancer tissues had expression levels less than 400. Therefore, there does not appear to be differential expression between the breast cancer tissues of Figure 3A and the 7 breast normal tissues of Figure 3C.

With respect to Figure 3B directed to colorectal cancer tissue, the expression level in the numerous tissues appears to range from 100-740 (no units provided). Turning to Figure 3C, normal colon appears to range from 100-200. 11 of the 78 (14%) colorectal tissues had expression levels less than 200. Therefore, the ranges of normal and cancerous expression levels of CHA4 overlap.

The art teaches what is called CHA4 in the specification has also been referred to as Ephrin-A3, EphA3, hek-L, Lerk-3, ehk1-L, and Ehk1. Beckmann et al. (US Pat. 5,516,658, May 1996) teaches Hek ligand (hek-L) polypeptides and nucleic acids encoding the polypeptides. The Hek-L polypeptides, SEQ ID NO: 2 of Beckmann and SEQ ID NO: 2 of the instant application are 100% identical over all 238 amino acids. The nucleic acid of Beckmann, namely SEQ ID NO: 1 and the instant SEQ ID NO: 1 share 52.7% identity over the full length with a best local similarity of 99.8% (see attached alignment). Beckmann teaches a human T-cell leukemia cell line expresses the Hek-L nucleic acid. Beckmann does not specifically teach using the Hek-L for diagnostic of cancers.

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. The specification and claims of the instant application assert that detection of the expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 allows for diagnosis of colorectal cancer. The evidence for this assertion provided in the specification, in Figure 3A-3D, Example 3, page 68, does not appear to support the assertion. As provided in the analysis above, the ranges for "normal" and "cancerous" tissue expression of CHA4 overlap in both breast and colon cancers analyzed. There is no indication in the specification of a threshold which would be indicative of colon or breast cancer tissue. Therefore, distinguishing a cancerous tissue from a normal tissue based solely on different sample expression would be unpredictable. While one could conduct additional experimentation to determine whether, e.g., expression of SEQ ID NO: 1 at certain levels might be associated with, e.g., certain types of colorectal or breast cancers, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. Specifically, 83% of the breast cancer tumors were within the "normal range."

Furthermore, the teachings of the prior art do not provide evidence of how to use the methods in which expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 are an indicator of breast or colorectal cancer. A nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 is not limited to any particular sequence, but comprises nucleic acid degenerates or fragments that encode part of SEQ ID NO: 2. The original claims were drawn to detecting a nucleic acid with at least 75% identity with SEQ ID NO: 1. The specification does not teach any analysis of

variants of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2. These variants may include variants which afford a protective effect to the nucleic acid such that they are indicative of lower risk for cancer. The variants also include splice-variants, SNPs, mutations, deletions, insertions which may have different diagnostic implications on the nucleic acids. Without undue and unpredictable experimentation, the skilled artisan would not be aware of which of the variants would have which effects on the risk of breast or colon cancers. It is unclear whether the nucleic acid encoding SEQ ID NO: 2, provided by Beckmann would have the same diagnostic effects as the instant SEQ ID NO: 1. As discussed briefly above, the specification asserts to have used an oligonucleotide array with T32108 as a probe. Based upon a visual inspection of T32108 appears to be most closely similar to nucleotides 1506-1690, while not 100% identical. Detection of nucleic acids which hybridize to T32108 is a much smaller class of compounds that nucleic acids which hybridize to a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2. Detection of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 encompasses nucleic acids which hybridize to the degenerate nucleic acid sequences of SEQ ID NO: 2. There is no indication that all of the degenerate nucleic acids sequences encoding SEQ ID NO: 2 would have the same diagnostics as T32108. Thus, since detection of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 is directed to nucleic acids non-specific hybridization would occur and would likely detect nucleic acid sequences which are not SEQ ID NO: 1 or T32108. The utility of the method is dependent on the specific nucleotide composition of the probe used to detect SEQ ID NO: 1 or nucleic acids that

encode an amino acid sequence of SEQ ID NO: 2. Degenerate coding sequences of any of these sequences, however, would not necessarily hybridize to SEQ ID NO 1 or would provide nonspecific hybridization such that the cancerous samples would not be differentiated from normal samples or any other tissue sample.

With respect to Claims 44-47, the specification does not teach how expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 are predictive of prognosis. The specification does not teach any levels of expression which provide extremely poor prognosis, as opposed to which levels of expression are deemed to be indicative of good prognosis. There are not thresholds or ranges which delineate any prognosis levels for individuals.

The teachings of the specification do not establish that one could actually detect expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 as an indicator of colorectal or breast cancer. Rather the teachings of the specification assert that a biochip comprising nucleotides 1506-1690 of SEQ ID NO: 1 illustrate expression at higher levels in the colon and breast tissue than in other human tissue types, as discussed above. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of a claimed invention. However, the closest prior art references, namely Beckmann, does not provide support for the use of expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 as an indicator of colorectal or breast cancer. Thus, it is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a

correlation or association between a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 expression and colorectal or breast cancer, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention.

Response to Arguments

The response traverses the rejection. The response attempts to support their assertions with respect to the ability of gene expression analysis as a means to diagnosis/prognosis of cancer by submitting "The National Cancer Institute Fact Sheet 5.18." It is noted that the NCI Fact Sheets has a date of November 6, 2002 on the bottom of the sheet and a review date of April 27, 1998. Thus, it is not entirely clear what date this sheet was available to the public. In the event that the sheet was not available to the public until after the filing date of the application, the information in the fact sheet would not support an enablement of the invention at the time of filing.

Regardless, this argument has been thoroughly reviewed, but is not found persuasive because the NCI Fact sheet states that "the main use of tumor markers is to assess a cancer's response to treatment and the check for recurrences." Thus, the NCI sheet does not seem to indicate that a cancer may be detected by a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2.

The response asserts "despite the presence of markers in normal tissue, the fact sheet states that detection of tumor/cancer makers provides a useful tool for the detection and diagnosis of some types of cancer when used along with x-rays or other

tests" (page 11, para 4 of response filed August2003). This argument has been reviewed but is not convincing because the instant specification does not provide any indication of how one would detect a tumor/cancer using the information provided in the specification. It is noted that the asserted novelty of the invention lies in the asserted overexpression of SEQ ID NO: 1 in cancers. The claims are broadly drawn to methods of comparing expression of nucleic acids in two samples to evaluate overexpression as a diagnostic of cancer. Therefore, the specification must enable the skilled artisan to detect cancer using overexpression. As previously provided, the specification teaches the overlapping ranges of normal and cancer expression of SEQ ID NO: 1, therefore, the skilled artisan would be required to perform additional experimentation to practice the invention as claimed.

The response points to examples of genes which have been highly studied, such as PSA, PAP, CA125, CEA, AFP etc, which are overexpressed in cancer. The response asserts that PSA is elevated in men with a malignant growth in the prostate, but may also be elevated in the blood of men with benign prostate conditions. The response states that "in checking PSA levels, doctors generally look for trends, such as steadily increasing PSA levels in multiple tests over time, rather than focusing on a single elevated result" (page 9, para 4 of the response filed December 2, 2002). This argument has been thoroughly reviewed, but is not found persuasive because the specification has stated that PSA is examined over time with trends rather than "focusing on a single elevated result" which appears to be precisely what was studied in

the instant specification. Therefore, the information regarding PSA is not analogous to the information provided in the instant specification.

The response provides that PAP is found at higher levels in some patient with prostate cancer, especially if the cancer has spread beyond the prostate. This gene is not analogous to the instant situation since, the ranges of normal do not overlap diseased. Similarly, CA125 is overexpressed in individuals with cancer and other conditions.

Based upon the assertions by the response and the knowledge in the art at the time the invention was made, the examiner acknowledges that some genes, once characterized, have diagnostic value in evaluating cancer and other conditions. However, the instant specification does not provide the skilled artisan with enough guidance to use the invention as claimed.

The response argues that the date in Figures 3A-3D adequately support the conclusion that elevated CHA4 expression levels relative to normal tissue levels correlates with the presence of breast or colorectal cancer (page 11 of response filed August2003). While the specification teaches that 85% of the colorectal cancer tissues had expression levels higher than any normal detection, the specification fails to provide any persuasive evidence with respect to breast cancer, where only 17% of the cancers had expression levels above normal. The examiner does not believe that the presence of an overexpression in 17% of the breast cancers is a significant result.
Thus, in overwhelming majority of the cancers tested, accurate results would not be observed. The response argues that only 2/7 normal breast tissue samples had levels

higher than 300. However, the instant specification and claims do not require any particular threshold for assigning samples as tumor or normal. The response further asserts that an average value would be more appropriate value to rely up, however, this means of detection is neither claimed nor contemplated in the instant specification. The claim merely recites comparing expression levels, therefore, in the event that the normal being compared to was above 300, incorrect detection would be made in 83% of the cases. The response also compares two of the normal samples with corresponding tumor samples and concludes that the levels were lower in normal tissue. The specification fails to provide evidence for the other 5 normal breast tissues with respect to the expression levels. Particularly, the highly expressed normal tissues, for example, Breast 100DOY and Breast-2. In the event that each of these is more highly expressed in tumors cells, a secondary consideration may be found. However, based upon the evidence as a whole in the specification, detecting breast cancer using this method would not enable the skilled artisan to make and use the invention at the time of filing.

The response asserts that Claims 44-47 have been amended to recite determine prognosis of the individual (page 12, response filed August 2003). This correlation has not been established in either the specification nor the art. The specification is completely silent with respect to poorer prognosis based upon the increased expression of CHA4 or a low level of expression as prognostic of poorer prognosis. The evidence of record, fails to provide any guidance with respect to prognosis based upon the detection of expression levels, for the reasons set forth above.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

7. No claims allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. After January 13, 2004, the examiner may be reached at 571-272-0743. The examiner can normally be reached Monday-Friday from 6:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196. After January, the receptionist may be reached at (571)272-0507

J. Goldberg

Jeanine Goldberg
Patent Examiner
December 19, 2003